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Title:

Renal apnoea: extreme disturbance of electrolyte and acid-base homoeostasis in an infant with Bartter syndrome type IV

Short title: Bartter IV

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Manuscript:

A two-week old infant was transferred to our renal ward from a district general neonatal intensive care unit following concerns of extreme acid-base and electrolyte disturbance from birth. The patient was born following spontaneous delivery at 32 weeks gestation. Severe polyhydramnios was noted antenatally and required two amniocenteses, removing a total of 6L fluid. She is the third child of consanguineous parents, with no significant medical problems reported in her siblings.

Initial investigations revealed a marked alkalosis: serum bicarbonate was 81mmol/L with a venous pH of 7.8. Biochemistry revealed a sodium of 116 mmol/L, potassium of 2.1 mmol, chloride of 59mmol/L and calcium of 1.99mmol/L. The patient demonstrated evidence of renal impairment with a urea of 20.8mmol/L and creatinine 146µmol/L. Examination was normal, except for a systolic ejection murmur. Subsequent echocardiography was unremarkable. Polyuria had been noted and the patient had been managed on fluid volumes of up to 200ml/kg/day prior to transfer. Weight was 1.68 kg (9th percentile), length: 44 cm (25th percentile) and head circumference 29 cm (5th percentile), blood pressure was normal at 68 mmHg systolic.

Given the constellation of hypokalaemic, hypochloraemic metabolic alkalosis, a presumptive diagnosis of Bartter syndrome was made. Electrolyte supplementation with sodium and potassium totaling 14 mmol/kg/day and 13 mmol/kg/day was provided. Despite this the patient had a persistent severe alkalosis (pH 7.56-7.92). Concerns regarding her respiratory drive were initially raised in the first week of her

admission, when she remained apneic after general anesthesia for a central line insertion and needed mechanical ventilation for 24 hours. In the first few months of life, the patient was noted to have repeated desaturations and subsequent polysomnography demonstrated prolonged periods of cyclical dips (73 dips/hour; normal <5) in oxygen saturation (SpO₂, see figure 1): with a mean and absolute nadir of 88% and 77%, respectively. Mean transcutaneous pCO₂ was raised at 75mmHg (10kPa), maximum 80mmHg, and a respiratory rate of 10 in periodic breathing, rising to 48 breaths/minute in Quiet Sleep. The Apnoea-Hypopnoea Index, a ratio of apneic episodes during hours slept, was 68 central events/hour (normal 0-4).

The patient remained polyuric with a urine output of 8-10ml/kg/h, leading to frequent episodes of dehydration with associated acute kidney injury (AKI). The highest recorded sodium was 176mmol/L, which improved with intravenous replacement of salt and water. Prostaglandin synthesis inhibitors, first indomethacin then celecoxib were trialed, but with minimal improvement and had to be frequently halted during episodes of AKI. Enteral feeds and salt supplementation were at times poorly tolerated and on one occasion led to hyponatraemic seizures (recorded sodium 94mmol/L).

Over the following year, she demonstrated profound global developmental delay with associated microcephaly and sensorineural hearing loss (confirmed by otoacoustic emissions and auditory brainstem response testing). She had evidence of chronic renal impairment from birth with an estimated GFR around 30ml/min/1.73m². The patient also developed severe hypophosphataemic rickets,

with plasma phosphate levels as low as 0.30 mmol/l, alkaline phosphatase levels as high as 1226 U/l (normal 80-345) and renal phosphate wasting ($TmP/GFR < 0.83 \text{ mmol/l}$; normal 1.10-2.70).

Given the serious clinical difficulties, which were chiefly attributed to the severe alkalosis, discussions were held about potential treatment approaches, including palliative care, bilateral nephrectomies with consequent renal replacement treatment, as well as titration with hydrochloric acid. At 10 months of age, a trial of amiloride was decided with the parents and the drug was slowly increased to 1mg/kg/day. Within weeks, plasma bicarbonate levels decreased to between 27-47 mmol/L, pH levels were persistently below 7.6, the patient's desaturations were less frequent, plasma phosphate levels normalized without supplementation and an improvement in general alertness was noted.

The patient was eventually discharged home after her first birthday, albeit with continuous jejunal feeds. She has shown some development, but remains severely delayed. Bloods at last follow-up reveal a serum bicarbonate of 31mmol/L (venous pH 7.54), potassium 4.0mmol/L, chloride 91mmol/L and creatinine of 86 $\mu\text{mol/L}$. Genetic testing confirmed Bartter syndrome type IV with a homozygous 1bp deletion in *BSND* (p.Pro151Leufs*27).

Bartter syndrome is a genetically heterogeneous condition characterized by failure of renal reabsorption of sodium and chloride in the thick ascending limb of Henle's loop, leading to insensible salt and water loss with consequent secondary

hyperaldosteronism¹. It is the increased mineralocorticoid activity that leads to the characteristic electrolyte profile of hypokalaemic metabolic alkalosis by enhancing potassium and proton secretion in the collecting duct in exchange for sodium reabsorption. Bartter syndrome type IV is caused by mutations in the *BSND* gene encoding Barttin, an essential subunit of the chloride channels CLCNKA and CLCNKB expressed in the loop of Henle, distal convoluted tubule and inner ear¹. Mutations in CLCNKB are the cause of Bartter syndrome type 3, typically of postnatal onset and without hearing loss, the so-called 'classic' Bartter syndrome. This milder presentation is presumably due to compensation by CLCNKA. In contrast, Bartter syndrome type IV is typically associated with a severe renal phenotype as well as hearing loss, as Barttin is a necessary subunit for both channels¹. The severity of metabolic derangement seen in this patient yet is even more pronounced than what has been reported before for this condition.

Metabolic alkalosis carries significant mortality: in adults, an arterial pH >7.55 is associated with a mortality rate of 45%, which rises to 80% if >7.65². Human studies have demonstrated a linear relationship between PaCO₂ and plasma bicarbonate. Respiratory suppression is the physiological response to alkalosis, an effect manifest through reduction in tidal volume. Ventilatory response to CO₂ is also blunted in metabolic alkalosis³.

The clinical finding of renal phosphate wasting leading to rickets has, to our knowledge, not been reported before as a complication of alkalosis in humans. Yet causality is likely, as renal phosphate wasting resolved with improved pH and

involved transporters are known to be pH dependent as phosphaturia due to alkalosis has been demonstrated in dogs⁴. Metabolic alkalosis has also been shown to depress plasma phosphorus levels in humans, although to a lesser degree than respiratory alkalosis⁵.

Most enzyme systems in our body are dependent on tight regulation of acid-base homeostasis and we presume that the initial obtunded state of our patient was also related to the extreme alkalosis, as it improved when venous pH levels decreased. Developmental delay is seen in neonatal Bartter phenotypes, which may in this case, have been compounded by the patient's prematurity, recurrent electrolyte instability, and episodes of acute on chronic kidney injury.

The treatment of Bartter syndrome with potassium-sparing diuretics, such as amiloride is potentially hazardous, as the mineralocorticoid activation is seen as a critical compensatory mechanism to minimise salt losses. Given that the kidneys regulate volume homeostasis through tubular salt handling, the mineralocorticoid-induced secretion of potassium and protons can be interpreted as the evolutionary primate of volume over acid-base and potassium homeostasis⁶. Given the severity of complications from the extreme alkalosis, we carefully commenced amiloride at a very low dose with subsequent up-titration, with close observation and concomitant sodium supplementation of more than 10mmol/kg/d to maintain volume homeostasis.

This case highlights the importance of the kidneys in maintaining homeostasis and the severe consequences for whole body physiology, if the underlying molecular mechanism is disrupted.

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